JAMA | Review

Systemic Amyloidosis Recognition, Prognosis, and Therapy
A Systematic Review

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IMPORTANCE Many patients with systemic amyloidosis are underdiagnosed. Overall, 25% of patients with immunoglobulin light chain (AL) amyloidosis die within 6 months of diagnosis and 25% of patients with amyloid transthyretin (ATTR) amyloidosis die within 24 months of diagnosis. Effective therapy exists but is ineffective if end-organ damage is severe.

OBJECTIVE To provide evidence-based recommendations that could allow clinicians to diagnose this rare set of diseases earlier and enable accurate staging and counseling about prognosis.

EVIDENCE REVIEW A comprehensive literature search was conducted by a reference librarian with publication dates from January 1, 2000, to December 31, 2019. Key search terms included *amyloid*, *amyloidosis*, *nephrotic syndrome*, *heart failure preserved ejection fraction*, and *peripheral neuropathy*. Exclusion criteria included case reports, non–English-language text, and case series of fewer than 10 patients. The authors independently selected and appraised relevant literature.

FINDINGS There was a total of 1769 studies in the final data set. Eighty-one articles were included in this review, of which 12 were randomized clinical trials of therapy that included 3074 patients, 9 were case series, and 3 were cohort studies. The incidence of AL amyloidosis is approximately 12 cases per million persons per year and there is an estimated prevalence of 30 000 to 45 000 cases in the US and European Union. The incidence of variant ATTR amyloidosis is estimated to be 0.3 cases per year per million persons with a prevalence estimate of 5.2 cases per million persons. Wild-type ATTR is estimated to have a prevalence of 155 to 191 cases per million persons. Amyloidosis should be considered in the differential diagnosis of adult nondiabetic nephrotic syndrome; heart failure with preserved ejection fraction, particularly if restrictive features are present; unexplained hepatomegaly without imaging abnormalities; peripheral neuropathy with distal sensory symptoms, such as numbness, paresthesia, and dysesthesias (although the autonomic manifestations occasionally may be the presenting feature); and monoclonal gammopathy of undetermined significance with atypical clinical features. Staging can be performed using blood testing only. Therapeutic decision-making for AL amyloidosis involves choosing between high-dose chemotherapy and stem cell transplant or bortezomib-based chemotherapy. There are 3 therapies approved by the US Food and Drug Administration for managing ATTR amyloidosis, depending on clinical phenotype.

CONCLUSIONS AND RELEVANCE All forms of amyloidosis are underdiagnosed. All forms now have approved therapies that have been demonstrated to improve either survival or disability and quality of life. The diagnosis should be considered in patients that have a multisystem disorder involving the heart, kidney, liver, or nervous system.

JAMA. 2020;324(1):79-89. doi:10.1001/jama.2020.5493

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Systemic amyloidosis is an uncommon disorder in which misfolded protein becomes resistant to the body's catabolic processes and fibrils deposit extracellularly within tissues, leading to organ dysfunction and death. Systemic amyloidosis is considered rare, but amyloidosis caused by 1 particular type of protein (ie, transthyretin [TTR]), known as amyloid TTR (ATTR) amyloidosis, is found in as many as 25% of adults older than 85 years on autopsy.[1,2] The incidence of immunoglobulin light chain (AL) amyloidosis is 12 cases per million persons per year.[3] Wild-type ATTR is estimated to have a prevalence 155 to 191 cases per million persons. The incidence of variant ATTR amyloidosis is estimated at 0.3 cases per year per million persons, with a prevalence estimate of 5.2 cases per million persons. Systemic amyloidosis results in a high symptom burden, impairment of quality of life, and a shortened survival.[4]

Amyloidosis is a multisystemic disorder that can affect the heart, kidneys, nerves, liver, lungs, and bowel. There are 14 proteins recognized that can form systemic amyloidosis. Reviewed here are the most common types of systemic amyloidosis: AL amyloidosis and ATTR amyloidosis.[5] There are more than 120 point variations in the TTR gene, most of which are rare, but the substitution of isoleucine with valine at position (ATTR V122I) is an amyloidogenic variation that exists in 3.5% of black individuals.[6] This variation can produce cardiac amyloidosis later in life.[6]

Literature Search

A search of MEDLINE, Scopus, PubMed, and EMBASE was conducted for English-language articles published from January 1, 2000, through December 31, 2019. Collection of relevant articles was facilitated with the Mayo Clinic Medical Library. The characteristics of the literature search criteria and the selection process are provided in the Supplement. The authors were responsible for selecting the articles for inclusion, and disagreements were resolved by negotiation. The following terms were used in the literature search: *amyloidosis*, *amyloid*, *restrictive cardiomyopathy*, *heart failure with preserved ejection fraction*, and *nondiabetic nephrotic syndrome*, *AL*, *TTR*, *transthyret* (wild-card search), *cardiac*, *wild*, *natural history*, *diagnosis*, *stage*, *clinical trial*, and *adult*. Duplicate articles were removed. Articles were classified as randomized clinical trials (12 involving 3074 patients), systematic reviews (n = 4), high-quality cohort studies (n = 3), case series (n = 9), or case reports (n = 0). A total of 81 references were included in this review.

Results

The literature search yielded 1769 high-quality full-text articles that were reviewed for inclusion. The majority of articles were cohort studies and case series because phase 3 clinical trials are extremely uncommon and limited to studies of therapies for amyloidosis. A total of 81 articles were selected for this review, of which 12 were randomized clinical trials of therapy that included 3074 patients, 9 were case series, and 3 were cohort studies (the remaining studies were phase 2 trials of therapy and reports of diagnostic methods).

Key Points

Question When should clinicians suspect and how should they diagnose systemic amyloidosis?

Findings Systemic amyloidosis should be suspected in patients with nondiabetic proteinuria, heart failure with preserved ejection fraction, unexplained peripheral neuropathy, or atypical monoclonal gammopathy of undetermined significance.

Meaning Late diagnosis of amyloidosis is a barrier to improved outcomes. Early recognition by primary care clinicians is vital for effective therapy to have a meaningful effect on survival.

Pathophysiology

All amyloid proteins are characterized by misfolding from the native α helical configuration to the proteolysis-resistant β pleated sheet. The inability to degrade these proteins results in their extracellular deposition of amyloid. TTR, the transporter of thyroxine- and retinol-binding protein, circulates as a stable tetramer. In ATTR amyloidosis, the tetramer becomes unstable and disassociates into monomers, which polymerize into amyloid fibrils. This instability can be a result of a point variation in the monomer or age-related instability of unmutated TTR. Systemic amyloidosis results from the deposition of an insoluble protein subunit that interferes with organ function.[7] In AL amyloidosis, the protein subunit is an immunoglobulin light or heavy chain fragment that can deposit in any organ, except the central nervous system, leading to organ dysfunction. The tetramer dissociates into a monomer, which misfolds into amyloid deposits. In ATTR amyloidosis, the heart is most commonly involved, with 70% of patients having peripheral neuropathy.[8] In variant forms of ATTR amyloidosis, the clinical phenotype is driven by the type of sequence variation. The most commonly recognized sequence variation worldwide presents with peripheral neuropathy (ATTR V30M).[9] The most common sequence variation seen in the US (ATTR T60A) has a dominant cardiomyopathy phenotype.[10] The ATTR V122I variation in black individuals is predominantly cardiac, although mild neuropathy may be present.

Symptoms

The clinical symptoms associated with AL amyloidosis are vague and nonspecific. They include fatigue, peripheral edema, weight loss, exertional dyspnea, and orthostatic hypotension.[11] In individuals with ATTR amyloidosis, the presentation includes palpitations (atrial fibrillation), dyspnea on exertion, and edema. These symptoms are vague (sensitive but not specific), and there are many disorders capable of producing similar symptoms that are far more common than systemic amyloidosis. In a survey of 459 patients with amyloidosis, only 26% reported that they were given the diagnosis of amyloidosis within 1 year of onset of symptoms, and 49% reported that they had seen 4 or more physicians prior to the establishment of a diagnosis.[12]

Signs

The signs in AL amyloidosis can be highly specific and include enlargement of the tongue and periorbital purpura (**Figure 1**); however, these occur in only 15% of patients and are not sensitive.[7] In wild-type ATTR amyloidosis, the noncardiac signs include bilateral

Figure 1. Physical Examination Findings Characteristic for Amyloid Disease

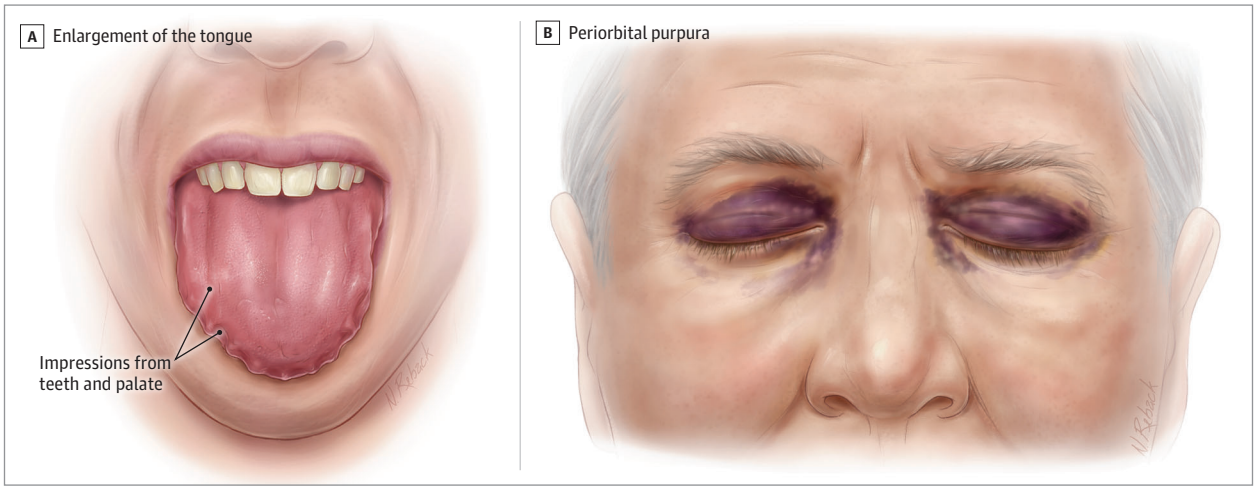


Table 1. Symptoms of Individuals Presenting With Systemic Amyloidosis

Symptom	Immunoglobulin light chain amyloidosis	Wild-type transthyretin amyloidosis	Variant transthyretin amyloidosis
Atypical MGUS or smoldering myeloma	X		
Diastolic dysfunction, HFpEF	X	X	X
Proteinuria, nondiabetic	X		
Small fiber neuropathy	X		X
Autonomic dysfunction	X		X
Hepatomegaly, no imaging defects	X		
Purpura on the face and/or neck	X		
Macroglossia	X		
Bilateral carpal tunnel	X	X	X
Spinal stenosis/pseudoclaudication	X	X	X
Biceps rupture		X	

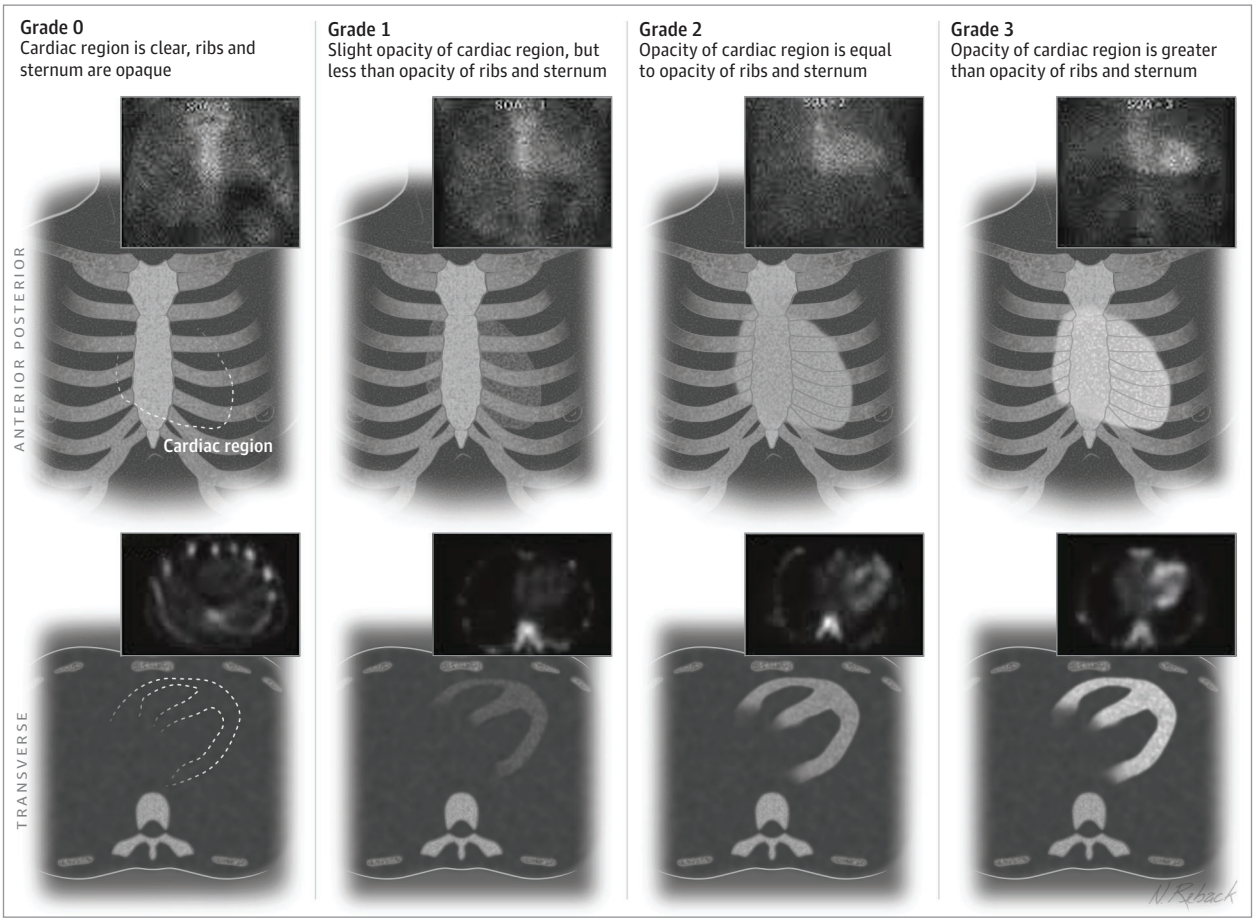
Abbreviations: HFpEF, heart failure with preserved ejection fraction; MGUS, monoclonal gammopathy of undetermined significance.

carpal tunnel syndrome, lumbar spinal stenosis,[13] and biceps tendon rupture.[14] Patients with variant ATTR amyloidosis will also have small fiber neuropathy and autonomic dysfunction.[15]

AL amyloidosis should be considered in any patient that has proteinuria without obvious explanations, such as longstanding hypertension or diabetes. The urinary sediment is bland, lacks casts, and shows fat and oval fat bodies.[16] The cardiac presentation of individuals with AL amyloidosis includes diastolic dysfunction, restriction to ventricular filling, and a low end-diastolic ventricular volume, resulting in reduced stroke volume and cardiac output. Cardiac amyloidosis is usually detected by echocardiography that shows concentric thickening of the left ventricle, which is often misdiagnosed as hypertrophy secondary to hypertension or hypertrophic cardiomyopathy. Because dysfunction is diastolic, systolic ejection fraction is normal until late into the disease, which makes it a classic form of heart failure with preserved ejection fraction.[17,18] Other echocardiographic features for individuals with cardiac amyloidosis include a rapid decline early in ventricular filling in diastole and abnormal apical longitudinal strain.[19,20] Cardiac magnetic resonance imaging can demonstrate ventricular wall thickening from infiltration and late gadolinium enhancement of the left ventricular wall.[21]

Patients with a symmetric neuropathy at the terminals of the longest nerves, which are in the lower legs and feet, sensory or mixed sensory-motor neuropathy characterized symptomatically by numbness paresthesia and dysesthesias (particularly those that have an associated monoclonal protein or autonomic dysfunction or bilateral carpal tunnel syndrome) are candidates for amyloidosis screening.[22,23] Patients with hepatomegaly with no imaging abnormalities and an elevated alkaline phosphatase should have amyloidosis included in the differential diagnosis, and AL amyloidosis should be considered in patients with atypical smoldering multiple myeloma or monoclonal gammopathy of undetermined significance with unusual features, such as weight loss, edema, and dyspnea in the absence of anemia. Deficiency of coagulation factor X is specific for AL amyloidosis and is believed to result from binding of the factor to the amyloid fibrils. Factor X deficiency is seen with equal frequency in kidney and hepatic amyloidosis. Factor X deficiency is very rare with cardiac or nerve presentations and is recognized in 7.5% of patients.[24] Serious bleeding is seen in 1% to 2% of individuals with factor X deficiency and can be recognized by prolongation of both the prothrombin time and partial thromboplastin time. Effective chemotherapy or stem cell transplant will normalize the levels of factor X. **Table 1** shows the most common presenting signs and syndromes in patients with systemic amyloidosis. In patients with AL amyloidosis, the heart is involved in 75% of cases, the kidney in 57%, the nerves in 22%, and the liver in 20%.[25] Gastrointestinal

Figure 2. Visual Grading of Cardiac Amyloid Transthyretin Amyloidosis Using ^{99m}Tc-Pyrophosphate Imaging



involvement is found in 17% of patients with AL amyloidosis. Within the first 6 months of diagnosis, 25% of patients die of end-stage organ failure related to advanced amyloid deposition.[25]

Approach to Diagnosis

Given the rarity of 12 cases per million individuals per year and the nonspecific symptoms of AL amyloidosis, it is impractical to perform an organ biopsy as a first test when the disorder is suspected. Ninety-nine percent of patients with AL amyloidosis have some form of immunoglobulin abnormality,[26] either the finding of a monoclonal protein on immunofixation of the serum or urine or an abnormal free light chain level, reflecting the underlying plasma cell dyscrasia that is responsible for production of light chains that misfold.[27] When a patient presents with a compatible syndrome and a light chain abnormality is detected, organ biopsy is not required because subcutaneous fat aspiration will demonstrate AL amyloid deposits in 78% to 100% of patients and lip biopsy will demonstrate AL amyloid deposits in 61% of patients[28]; a bone marrow biopsy, which is generally done once an immunoglobulin light chain abnormality is detected, will be demonstrate amyloid deposits in 57% of patients.[29] Direct organ biopsy should be considered only if the index of suspicion is very high.[30]

For ATTR cardiac amyloidosis, a biopsy may not be required. If a patient has a echocardiogram findings that demonstrate features consistent with amyloidosis of the heart, a technetium pyrophosphate scan or technetium 3,3-diphosphono-1,2-propanodicarboxylic acid (DPD) scan can be used to diagnose ATTR cardiac amyloidosis. Visual grading is done by comparing cardiac and rib uptake. Grade 0 indicates no uptake in heart, grade 1 indicates uptake in the heart less than uptake in rib, grade 2 indicates heart uptake equal to the rib, and grade 3 indicates heart uptake greater than the rib (**Figure 2**). A biopsy is not required if there is no associated immunoglobulin light chain abnormality suggesting the possibility of AL amyloidosis.[31] If ATTR amyloidosis is suspected based on results of a radionuclide scan of the heart positive for uptake of the injected radionuclide, suggesting ATTR amyloidosis, genetic testing is required to exclude an inherited variant of ATTR. This is generally done by polymerase chain reaction sequencing of the TTR gene. In patients with a positive ^{99m}Tc-pyrophosphate (PYP) scan and an immunoglobulin abnormality, tissue proof of amyloidosis with mass spectroscopic confirmation is currently recommended.

Indications for Biopsy

When results of a tissue biopsy demonstrate amyloidosis, it is imperative that the protein subunit be accurately identified. The major diagnostic tools available for the diagnosis of amyloidosis are shown in **Box 1**. Amyloid protein typing can be done by immunochemical classification of the amyloid using antisera directed at the precursor proteins, but this is only reliable in the most expert

amyloid pathology laboratories. Mass spectroscopy is considered the current reference standard of classification of amyloid.[32] Using this technique, amyloid deposits are laser-dissected from amyloid-containing tissue and the microdissected amyloid fragments undergo sorting based on molecular weight. Peptides common to all forms of amyloidosis are used as positive controls, including serum amyloid P component, apolipoprotein A4, and apolipoprotein E. Peptide sequences are compared with a library of sequences to assist in protein identification. In a series of 142 amyloid-laden tissues, nonspecific immunostaining was seen in 34 of the amyloid-laden tissues (24%), in which the type of amyloidosis could not be classified. Using mass spectroscopy, inconclusive results were seen in only 9 amyloid-laden tissues (6%), reflecting the enhanced sensitivity of proteomic analysis.[33] Mass spectroscopic detection of AL amyloidosis does not prove that the amyloidosis is systemic because localized forms of amyloidosis commonly involving the skin, larynx, lung nodules, genitourinary tract, and the edges of bowel or stomach ulcers occur and may be composed of light chains.[34] A monoclonal protein can be found in 23% of patients with ATTR amyloidosis, and the presence of amyloid biopsy results positive for amyloid deposits in the heart and a monoclonal gammopathy should not be considered diagnostic of AL amyloidosis without further classification by proteomics or immunohistochemistry, because these patients may have AL or ATTR amyloidosis.[35]

Staging

Once a diagnosis of amyloidosis is established, prognosis should be assessed. There are a number of risk models used for AL amyloidosis.[36] The Mayo Clinic 2004 model classifies patients into 3 stages. Threshold values are cardiac troponin T less than 0.035 µg/L and N-terminal fragment of the prohormone brain natriuretic peptide (NT-proBNP) less than 332 ng/L. Patients are considered to have stage I AL amyloidosis when both cardiac troponin T and NT-proBNP are below the threshold values, stage II if only 1 marker is below the threshold values, and stage III if both are equal to or above the threshold values. Using the troponin T or high-sensitivity troponin T markers of myocardial cell injury and the NT-proBNP natriuretic peptides produced by the myocardial cells, in response to stimulation of cardiac stretch receptors and increased wall tension, NT-proBNP is elevated in heart failure and highly sensitive for cardiac involvement in amyloidosis, can provide prognostic information on outcomes. The 2015 European modification of the Mayo Clinic 2004 model adds a fourth category based on whether NT-proBNP is greater than 8500 pg/mL. The Mayo 2012 model classifies patients based on the troponin T or high-sensitivity troponin T, NT-proBNP, and the difference between the involved and the uninvolved free light chain (dFLC) value. All models had a similar predictive value for survival (**Table 2**).[37-39] The expected number of deaths was calculated for each patient in each model given their covariate value and follow-up time. A difference in survival prediction between models of less than 5% was considered to represent no change. These comparisons were summarized by the number of patients for which the model of interest provided better prediction of death in those who died and better prediction of survival in those who survived. The 2004 model better predicts for early death and the 2012 model has a better prediction for long-term survival. The prognosis of AL amyloidosis can be determined by 2 or 3 simple blood tests.[40] Wild-type ATTR amyloidosis has a median overall survival of 3.6 years. The staging system that exists relies on the NT-proBNP and serum troponin levels, resulting in 3 stages with 4-year overall survival of 57% for stage I, 42% for stage II, and 18% for stage III.[41] A staging system that uses estimated glomerular filtration rate (eGFR) and NT-proBNP in ATTR amyloidosis, in which stage I is defined as NT-proBNP less than or equal to 3000 ng/L and eGFR greater than or equal to 45 mL/min, stage III as NT-proBNP greater than 3000 ng/L and eGFR less than 45 mL/min, and stage II as meeting neither the criteria for stage I or III, reported median survival of 69.2 months for patients with stage I ATTR, 46.7 months for patients with stage II ATTR,

Box 1. Major Diagnostic Tools Available for Amyloidosis

Serum immunofixation
- Useful in detecting a monoclonal protein raising suspicion of immunoglobulin light chain (AL) amyloidosis

Urine immunofixation
- Useful in detecting a monoclonal protein raising suspicion of AL amyloidosis

Serum immunoglobulin free light chain
- Useful in detecting a monoclonal protein raising suspicion of AL amyloidosis

Echocardiography with left ventricular longitudinal strain
- Findings of wall thickening, impaired relaxation, and abnormal strain consistent with infiltrative cardiomyopathy amyloidosis; not seen with ischemia or valve disease

Cardiac magnetic resonance imaging
- Demonstrates wall thickening; late gadolinium enhancement specific for amyloidosis

Technetium pyrophosphate or methylene diphosphonate scintigraphy (cardiac amyloid transthyretin [ATTR] amyloidosis only)
- Uptake in myocardium seen in ATTR amyloidosis; diagnostic if no monoclonal gammopathy (mass spectroscopy is required if there is monoclonal gammopathy and a positive PYP scan)

Subcutaneous fat aspiration for Congo red staining
- Least invasive technique to obtain tissue biopsy verification of amyloidosis

Bone marrow biopsy, Congo red staining, and fluorescence in situ hybridization (FISH) genetics
- Alternate source of tissue for tissue verification of amyloidosis; required to exclude myeloma in AL amyloidosis; FISH genetics prognostic for outcomes in AL amyloidosis

Lip biopsy for Congo red staining
- Alternate noninvasive tissue source for demonstrating amyloid deposits

N-terminal fragment of the prohormone brain natriuretic peptide
- Cardiac biomarker used in staging of all forms of amyloidosis

Troponin
- Cardiac biomarker used in staging of all forms of amyloidosis

Amyloid typing with tissue mass spectrometry or immunohistochemistry completed by very experienced clinicians
- Required for all positive Congo red tissue specimens to verify the subunit protein composition

Germline DNA testing (transthyretin and other rare hereditary amyloid precursor proteins)
- Required to distinguish wild-type ATTR from variant ATTR amyloidosis

Table 2. Staging Systems for Immunoglobulin Light Chain Amyloidosis

	Threshold			Survival			
Staging system	NT-proBNP, pg/mL	Troponin T, ng/mL	dFLC, mg/L	Stage I	Stage II	Stage III	Stage IV
				Median survival, mo			
Mayo 2004	332	0.035		27.2	11.1	4.1	
Mayo 2012	1800	0.025	180	94.1	40.3	14	5.8
				Survival at 3 y, %			
European 2016	332	.035		100	52	55	19 (NT-proBNP >8500)

Abbreviations: dFLC, difference between the involved and the uninvolved free light chain; NT-proBPN, N-terminal fragment of the prohormone brain natriuretic peptide.

and 24.1 months for patients with stage III ATTR.[42] A suggested approach to diagnostic testing to establish a diagnosis of amyloidosis is shown in **Figure 3**. The 2012 model appears to be used most in clinical practice and is the only staging system listed in the National Comprehensive Cancer Network guidelines on amyloidosis.

Management of AL Amyloidosis

Substantial controversy exists about the treatment of patients with AL amyloidosis. Common management approaches are anti–plasma cell systemic chemotherapy and high-dose chemotherapy followed by autologous stem cell transplant (**Box 2**). The first phase 3 study that compared the effect of chemotherapy with transplant in 100 patients with AL amyloidosis was inconclusive because of very high therapy-related mortality associated with stem cell transplant (9 deaths among 37 patients) and because 26% of patients assigned to undergo stem cell transplant did not.[43] However, observational studies showed that from 2010 to 2016, the median overall survival for patients who underwent stem cell transplant was 10 years.[44] These were optimal results obtained from a highly select group of patients that excluded patients with advanced heart failure, significant kidney impairment, functional impairment of performance, and advanced age. Only 20% to 25% of patients with AL amyloidosis are considered eligible for stem cell transplant based on age, kidney function, and severity of heart failure.[45,46]

Conventional chemotherapy is administered to most patients with AL amyloidosis. Plasma cells are targeted for elimination by chemotherapy because they are responsible for synthesis of immunoglobulin light chains, which are precursors for amyloid deposits. Many of the regimens used for amyloid management were derived from multiple myeloma treatments. In a case series of 46 patients treated with melphalan and dexamethasone, long-term follow-up demonstrated that a median overall survival of 5 years was achieved with this simple oral regimen that can be administered to patients with significant degrees of cardiac, kidney, and hepatic dysfunction.[47] A phase 3 trial that compared melphalan-dexamethasone-bortezomib vs melphalan-dexamethasone in 110 patients with newly diagnosed amyloidosis showed significant improvements in both progression-free and overall survival with the bortezomib-containing regimen, including a greater overall hematologic response and significantly greater partial response (42% vs 20% of participants had a partial response).[48] The value of deeper responses (complete, very good partial, and partial) in predicting survival has been validated repeatedly.[49] In a nonrandomized multicenter trial of 230 patients, bortezomib was combined with cyclophosphamide and dexamethasone and yielded a median overall survival of 6 years and a 5-year survival of 80%, with a 2-year survival of 90% for complete responders and 68% for very good partial responders.[50] In the US, cyclophosphamide-bortezomib-dexamethasone appears to be the most commonly used regimen for managing AL amyloidosis.[46] The oral proteasome inhibitor ixazomib, given with dexamethasone, was compared with physicians' choice of standard care in a phase 3 trial of 168 patients and demonstrated hematologic responses in 45 patients (53%) vs 42 patients (51%) receiving standard care. Higher complete response rates were seen with ixazomib-dexamethasone than with standard care (26% vs 18%). Vital organ response rates were 36% in the ixazomib-dexamethasone group vs 11% in the standard care group (cardiac response rate: 18% vs 5%; kidney response rate: 28% vs 7%).[51,52] Pomalidomide has been used as second-line therapy for patients with AL amyloidosis but is not well tolerated in patients with cardiac amyloidosis.[53]

Genetics can help predict therapy-related outcomes. Fluorescence in situ hybridization genetics show a t(11;14) sequence variation in approximately 50% of patients with amyloidosis. These patients appear to have lower response rates and shorter survival when exposed to bortezomib-containing regimens.[54] The incorporation of alkylator, either melphalan or cyclophosphamide, in the regimen is important for these patients.[55] Patients with t(11;14) had a higher complete response rate in response to melphalan than patients who did not have t(11;14) (28 of 68 [41.2%] vs 9 of 46 [20.0%]; $P = .02$). Patients with t(11;14) also express BCL-2, and trials examining the effect of a BCL-2 inhibitor, venetoclax, in the management of AL amyloidosis are underway (ClinicalTrials.gov NCT03000660).[56]

Daratumumab is a monoclonal antibody directed at the CD38 antigen found uniformly on plasma cells and is approved for the management of both newly diagnosed and relapsed multiple myeloma. Several retrospective series and 2 phase 2 trials have demonstrated that daratumumab was associated with response rates ranging from 63% to 100% in patients who underwent chemotherapy and stem cell transplant and relapsed or did not respond to the last-administered chemotherapy regimen.[57,58] Currently, a phase 3 randomized clinical trial is being performed that compares daratumumab given with cyclophosphamide-bortezomib-dexamethasone vs cyclophosphamide-bortezomib-dexamethasone alone in 417 newly diagnosed untreated patients with AL amyloidosis (ClinicalTrials.gov NCT03201965).[59] In a preliminary report of 28 patients with a median (range) treatment duration of 11 (0.2-14) months, the response rate was 96% in the daratumumab group, with 82% achieving a very good partial

response or better; 36% of patients achieved a complete hematologic response.[60]

Goals of Therapy

Treatment efficacy is determined by established criteria for hematologic and organ responsiveness.[61] Declining levels of immunoglobulin free light chain are the goal for AL amyloidosis therapy. A partial response is defined as a 50% reduction in the dFLC, a very good partial response is considered present when there is a 90% decline in dFLC or an absolute dFLC less than 4 mg/dL, and a complete response occurs if the dFLC level is within the normal ragnge.[61] When the baseline free light chain is less than 5 mg/dL, a dFLC goal of less than 1 mg/dL yields the best survival outcomes.[62] The hematologic response criteria are strongly correlated with survival benefit.[63] Organ response is defined by consensus guidelines, such as having reductions in NT-proBNP levels for individuals with cardiac amyloidosis, reduced urinary protein loss for individuals with kidney disease, and reduced alkaline phosphatase levels for individuals with liver amyloidosis.[64] Amyloid neuropathy can be assessed by the modified Neuropathy Impairment Score +7, although this test is not used in clinical practice but is used for drugs being evaluated for US Food and Drug Administration approval for amyloid neuropathy treatment.[65]

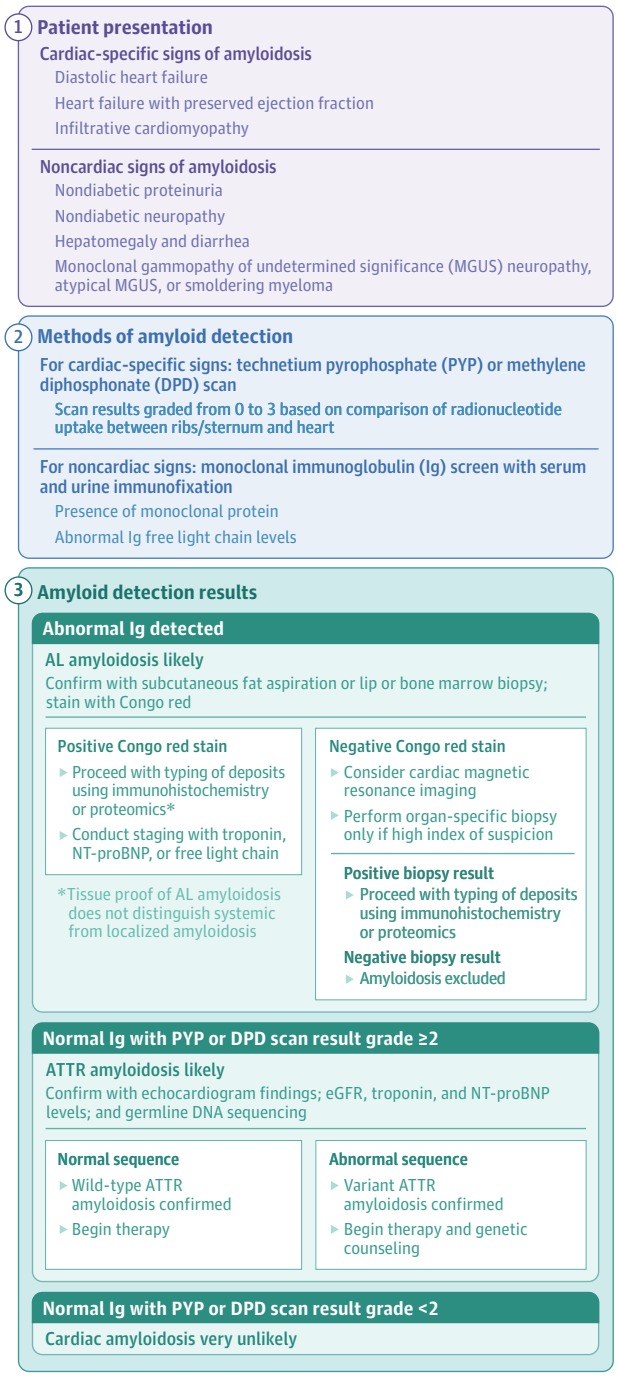
Antiplasma cell chemotherapy does not remove established deposits of amyloid. There has been longstanding interest in developing antibodies capable of dissolving existing deposits of amyloid in the hope that it would lead to improvement of organ function independent of the hematologic response. A trial of an antifibril antibody was terminated based on a futility analysis predicting inability to achieve prespecified cardiac end points.[66]

Management of ATTR Amyloidosis

Tafamidis is an oral agent with a low toxicity profile that prevents the destabilization of the TTR tetramer, preventing the formation of monomers that polymerize into the amyloid fibril.[67] In a double-blind, placebo-controlled, phase 3 trial that enrolled 441 patients with both cardiac wild-type ATTR and variant ATTR, tafamidis improved the composite outcome of all-cause mortality and hospitalization for cardiac failure and resulted in a 30% reduction in the composite outcome compared with placebo. Tafamidis was associated with lower all-cause mortality than placebo (78 of 264 patients [29.5%] vs 76 of 177 patients [42.9%]; hazard ratio, 0.70 [95% CI, 0.51-0.96]) and a lower rate of cardiovascular-related hospitalizations (0.48 per year vs 0.70 per year; relative risk ratio, 0.68 [95% CI, 0.56-0.81]).[68] A 2019 phase 2 trial of an antimisfolding agent, AG10, that enrolled 49 patients demonstrated the ability of this molecule to stabilize the tetramer and maintain higher levels of transthyretin in the circulation.[69] Average serum TTR increased by 36% ± 21% when 400 mg of AG10 was administered and 51% ± 38% with 800 mg of AG10 (both $P < .0001$ vs placebo). Baseline serum TTR in treated subjects was below normal in 80% of participants with variant ATTR and 33% of participants with wild-type ATTR. AG10 treatment restored serum TTR to the normal range in all participants.[69]

Previously, liver transplant was the only effective therapy for individuals with variant ATTR amyloidosis,[70] which usually did not stop disease progression. Diflunisal, a nonsteroidal anti-inflammatory agent, was shown to reduce the progression of variant ATTR polyneuropathy over time in a phase 3 randomized placebo-controlled trial that enrolled 130 patients, but the drug is not approved by the US Food and Drug Administration for this indication.[71] Inotersen, an antisense oligonucleotide, and Patisiran, a small interfering RNA, act by preventing the translation of TTR messenger RNA and are approved by the US Food and Drug Administration for the management of amyloidosis. Both agents

Figure 3. Diagnostic Algorithm for Systemic Amyloidosis



AL indicates immunoglobulin light chain; ATTR, amyloid transthyretin; eGFR, estimated glomerular filtration rate; NT-proBNP, N-terminal fragment of the prohormone brain natriuretic peptide.

Box 2. Major Therapies Available for Individuals With Amyloidosis

Immunoglobulin light chain amyloidosis
Stem cell transplant (20%-25% of patients are eligible)
Bortezomib-melphalan-dexamethasone
Cyclophosphamide-bortezomib-dexamethasone
Daratumumab-based therapy
Bortezomib-dexamethasone
Pomalidomide-dexamethasone
Lenalidomide-dexamethasone
Venetoclax (clinical trial)

Wild-type amyloid transthyretin (ATTR) amyloidosis
Tafamidis
AG10 (investigational)

Variant ATTR amyloidosis
Patisiran (peripheral neuropathy)
Inotersen (peripheral neuropathy)
Tafamidis (cardiac in US; cardiac or nerve in Europe)
Diflunisal (off-label use for variant ATTR amyloid neuropathy)
Liver transplant

reduced circulating levels of TTR by 70% in a follow-up of 15 months and to 80% in a follow-up of 18 months and demonstrated a significant slowing of the progression of the disease, measured by the neurologic impairment score and improved quality of life.[72,73] These trials were not designed to assess the effect on cardiac function, and both agents are only approved for individuals with variant ATTR amyloidosis peripheral neuropathy. Patient with advanced neurologic disability or prior liver transplant were excluded from these trials. These agents are now being tested in trials specifically designed to test the safety and efficacy in patients with cardiac ATTR amyloidosis.

Discussion

Because therapy that is effective and improves survival and quality of life for all forms of systemic amyloidosis is now available, it is important not to overlook this diagnosis. Proteinuria, unexplained dyspnea on exertion, and progressive small fiber neuropathy suggests the need to evaluate a patient for amyloidosis.[74] Patients with kidney, hepatic, or peripheral nerve dysfunction should be screened for AL amyloidosis with immunofixation of the serum and urine and a serum immunoglobulin free light chain assay. The finding of an abnormal light chain is followed by further tissue examination by fat aspiration, bone marrow biopsy, or lip biopsy.[75] If all of these tests are negative for the presence of amyloid deposits, amyloidosis can be excluded in 85% of patients.[51] Unless the index of suspicion is high, the evaluation can be discontinued at this point. For those patients who do not have an abnormal immunoglobulin free light chain result, AL amyloidosis is unlikely. However, if the index of suspicion is high, a biopsy of an affected organ is indicated. For patients who present with heart failure with preserved ejection fraction, both echocardiography (or cardiac magnetic resonance imaging) and cardiac pyrophosphate or DPD scanning should be performed.[76] In patients that have a PYP or DPD scan with results negative for radionuclide uptake in the myocardium, cardiac ATTR amyloidosis is very unlikely. Cardiac magnetic resonance imaging could be considered to improve a clinician's index of suspicion if echocardiography is equivocal. In the presence of a high index of suspicion, endomyocardial biopsy is justified.[8] Once an amyloid-laden tissue is detected, typing with mass spectrometry or immunohistochemistry is required to ensure that the type of amyloid is validated. All patients with a PYP or DPD scan with results positive for radionuclide uptake in the myocardium require germline DNA testing to look for a sequence variation in the TTR molecule.[77] The false-negative rate of organ biopsy (eg, heart, kidney, liver) results is negligible,[78] and if results of a targeted biopsy are negative for amyloid deposition, the diagnosis should no longer be pursued.

For patients with a sequence variation in the TTR gene, referral to a genetic counselor to discuss the potential of screening all first-degree family members is important.[79] Patients who have peripheral neuropathy and an inherited variation should have a discussion of the 2 available therapies that lower the translation of TTR messenger RNA.

Patients diagnosed with AL amyloidosis should be assessed for stem cell transplant eligibility. A discussion of the risks and benefits of high-dose chemotherapy and stem cell transplant, including the lack of high-quality outcomes information demonstrating a survival advantage, should be discussed. For patients who wish to proceed with stem cell transplant and have more than 20% plasma cells in the bone marrow or have symptomatic myeloma or high-risk genetics, induction chemotherapy is given, which is generally bortezomib-based, for 2 to 4 months.[80] Patients who do not fulfill criteria for multiple myeloma with less than 10% bone marrow plasma cells and no myeloma bone disease can undergo stem cell transplant without induction therapy.[81] In all instances, the goal of therapy is a hematologic very good partial response at minimum. Patients who do not achieve a very good partial response should be considered for consolidation chemotherapy because the best outcomes are associated with involved light chain levels of less than 1 mg/dL. For patients who are not eligible to undergo transplant, the recommendation is for bortezomib-based chemotherapy designed to produce a very good partial response or better.[82] For those patients who achieve a very good partial response, maintenance treatment with bortezomib chemotherapy should be considered. Patients who present initially with a low tumor mass likely can be observed after a response is achieved with initial therapy. These recommendations are derived from expert opinion found in consensus guidelines and are not based on high-quality clinical trials.

No consensus exists for when to resume therapy for relapsed AL amyloidosis and how to manage it. If prior treatments were not daratumumab based, treating individuals who have relapsed with these agents is a reasonable option. If the hematologic relapse occurred more than 2 years after the last therapy, repeating the original treatment regimen is a consideration. For patients who are not bortezomib refractory, bortezomib combined with steroid alone or cyclophosphamide or melphalan is an option. For patients who are refractory to treatment with bortezomib and

who have not achieved a hematologic response with daratumumab, immunomodulatory-based therapy is reasonable. Although data are limited, use of carfilzomib or venetoclax-based therapies could be considered.

There are several limitations to this article. First, given the rarity of systemic amyloidosis, there is a lack of high-quality trials to define optimal therapy. Second, no systematic population studies exist to determine how often the diagnosis is overlooked. Third, most guidelines on diagnosis of amyloidosis and therapy are based on single institutional case series and expert consensus.

Conclusions

Improvements in outcomes for individuals with systemic amyloidosis are affected by delays in diagnosis as a consequence of failure to recognize the syndromes. Early diagnosis of AL amyloidosis allows for effective chemotherapy to improve organ function. When ATTR amyloidosis is recognized before advanced organ dysfunction develops, quality of life could be improved using gene silencers or stabilizers.

ARTICLE INFORMATION

Accepted for Publication: March 30, 2020.

Author Contributions: Drs Gertz and Dispenzieri had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: All authors.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: All authors.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Dispenzieri.
Administrative, technical, or material support: All authors.
Supervision: Gertz.

Conflict of Interest Disclosures: Dr Gertz reported receiving personal fees from Akccea, Alnylym, Prothena, Janssen, Spectrum, Apellis, Amgen, Physicans Education Resource, Research to Practice, Johnson and Johnson, Proclara, and i3Health outside the submitted work and serving on data and safety monitoring boards for AbbVie and Celgene and receiving royalties from Springer Publishing, grant funding to the institution from the Amyloidosis Foundation and the Macroglobulinemia Foundation (NCI SPORE MM SPORE 5P50 CA186781-04), and personal fees from Sanofi. Dr Dispenzieri reported receiving grants from Celgene, Takeda, Alnylam, Prothena, and Pfizer and personal fees from Intellia and Akcea outside the submitted work.

Additional Contributions: We would like to recognize Patricia Erwin, MLS (Mayo Alix School of Medicine), for expert search services. Ms Erwin was not compensated for her contribution.

Submissions: We encourage authors to submit papers for consideration as a Review. Please contact Edward Livingston, MD, at Edward.livingston@jamanetwork.org or Mary McGrae McDermott, MD, at mdm608@northwestern.edu.

REFERENCES

1. Ueda M, Horibata Y, Shono M, et al. Clinicopathological features of senile systemic amyloidosis: an ante- and post-mortem study. *Mod Pathol*. 2011;24(12):1533-1544. doi:10.1038/modpathol.2011.117

2. Tanskanen M, Peuralinna T, Polvikoski T, et al. Senile systemic amyloidosis affects 25% of the very aged and associates with genetic variation in alpha2-macroglobulin and tau: a population-based autopsy study. *Ann Med*. 2008;40(3):232-239. doi:10.1080/07853890701842988

3. Kyle RA, Larson DR, Kurtin PJ, et al. Incidence of AL amyloidosis in Olmsted County, Minnesota, 1990 through 2015. *Mayo Clin Proc*. 2019;94(3):465-471. doi:10.1016/j.mayocp.2018.08.041

4. Lin HM, Gao X, Cooke CE, et al. Disease burden of systemic light-chain amyloidosis: a systematic literature review. *Curr Med Res Opin*. 2017;33(6):1017-1031. doi:10.1080/03007995.2017.1297930

5. Benson MD, Buxbaum JN, Eisenberg DS, et al. Amyloid nomenclature 2018: recommendations by the International Society of Amyloidosis (ISA) nomenclature committee. *Amyloid*. 2018;25(4):215-219. doi:10.1080/13506129.2018.1549825

6. Buxbaum JN, Ruberg FL. Transthyretin V122I (pV142I)* cardiac amyloidosis: an age-dependent autosomal dominant cardiomyopathy too common to be overlooked as a cause of significant heart disease in elderly African Americans. *Genet Med*. 2017;19(7):733-742. doi:10.1038/gim.2016.200

7. Merlini G, Dispenzieri A, Sanchorawala V, et al. Systemic immunoglobulin light chain amyloidosis. *Nat Rev Dis Primers*. 2018;4(1):38. doi:10.1038/s41572-018-0034-3

8. Siddiqi OK, Ruberg FL. Cardiac amyloidosis: an update on pathophysiology, diagnosis, and treatment. *Trends Cardiovasc Med*. 2018;28(1):10-21. doi:10.1016/j.tcm.2017.07.004

9. Suhr OB, Gustavsson S, Heldestad V, et al. New insights into the clinical evaluation of hereditary transthyretin amyloidosis patients: a single center's experience. *Degener Neurol Neuromuscul Dis*. 2012;2:93-106. doi:10.2147/DNND.S24652

10. Sattianayagam PT, Hahn AF, Whelan CJ, et al. Cardiac phenotype and clinical outcome of familial amyloid polyneuropathy associated with transthyretin alanine 60 variant. *Eur Heart J*. 2012;33(9):1120-1127. doi:10.1093/eurheartj/ehr383

11. Di Girolamo M, Monno D, Pirro MR, Nowakowski M. Approach to diagnosis in systemic amyloidosis: initial findings and time from symptoms onset to diagnosis (light-chain amyloidosis vs. transthyretin): problems and observations. *Amyloid*. 2011;18(suppl 1):83-85. doi:10.3109/13506129.2011.574354030

12. Lousada I, Comenzo RL, Landau H, Guthrie S, Merlini G. Light chain amyloidosis: patient experience survey from the amyloidosis research consortium. *Adv Ther*. 2015;32(10):920-928. doi:10.1007/s12325-015-0250-0

13. Carr AS, Shah S, Choi D, et al. Spinal stenosis in familial transthyretin amyloidosis. *J Neuromuscul Dis*. 2019;6(2):267-270. doi:10.3233/JND-180348

14. Barge-Caballero G, López-Bargiela P, Pombo-Otero J, Pardo-Martínez P. Quadriceps tendon rupture in wild-type transthyretin amyloidosis (ATTRwt). *Eur Heart J*. 2019;40(16):1307. doi:10.1093/eurheartj/ehz128

15. Cortese A, Vegezzi E, Lozza A, et al. Diagnostic challenges in hereditary transthyretin amyloidosis with polyneuropathy: avoiding misdiagnosis of a treatable hereditary neuropathy. *J Neurol Neurosurg Psychiatry*. 2017;88(5):457-458. doi:10.1136/jnnp-2016-315262

16. Engineer DP, Kute VB, Patel HV, Shah PR. Clinical and laboratory profile of renal amyloidosis: a single-center experience. *Saudi J Kidney Dis Transpl*. 2018;29(5):1065-1072. doi:10.4103/1319-2442.243966

17. Ritts AJ, Cornell RF, Swiger K, Singh J, Goodman S, Lenihan DJ. Current concepts of cardiac amyloidosis: diagnosis, clinical management, and the need for collaboration. *Heart Fail Clin*. 2017;13(2):409-416. doi:10.1016/j.hfc.2016.12.003

18. Mohammed SF, Mirzoyev SA, Edwards WD, et al. Left ventricular amyloid deposition in patients with heart failure and preserved ejection fraction. *JACC Heart Fail*. 2014;2(2):113-122. doi:10.1016/j.jchf.2013.11.004

19. Di Nunzio D, Recupero A, de Gregorio C, Zito C, Carerj S, Di Bella G. Echocardiographic findings in cardiac amyloidosis: inside two-dimensional, doppler, and strain imaging. *Curr Cardiol Rep*. 2019;21(2):7. doi:10.1007/s11886-019-1094-z

20. Cappelli F, Baldasseroni S, Bergesio F, et al. Echocardiographic and biohumoral characteristics in patients with AL and TTR amyloidosis at diagnosis. *Clin Cardiol*. 2015;38(2):69-75. doi:10.1002/clc.22353

21. Oda S, Utsunomiya D, Nakaura T, et al. Identification and assessment of cardiac amyloidosis by myocardial strain analysis of cardiac magnetic resonance imaging. *Circ J*. 2017;81(7):1014-1021. doi:10.1253/circj.CJ-16-1259

22. Finsterer J, Iglseder S, Wanschitz J, Topakian R, Löscher WN, Grisold W. Hereditary transthyretin-related amyloidosis. *Acta Neurol Scand*. 2019;139(2):92-105. doi:10.1111/ane.13035

23. Sperry BW, Reyes BA, Ikram A, et al. Tenosynovial and cardiac amyloidosis in patients undergoing carpal tunnel release. *J Am Coll Cardiol*. 2018;72(17):2040-2050. doi:10.1016/j.jacc.2018.07.092

24. Thompson CA, Kyle R, Gertz M, Heit J, Pruthi R, Pardanani A. Systemic AL amyloidosis with acquired factor X deficiency: a study of perioperative bleeding risk and treatment outcomes in 60 patients. *Am J Hematol*. 2010;85(3):171-173. doi:10.1002/ajh.21603

25. Muchtar E, Gertz MA, Kyle RA, et al. A modern primer on light chain amyloidosis in 592 patients with mass spectrometry-verified typing. *Mayo Clin Proc*. 2019;94(3):472-483. doi:10.1016/j.mayocp.2018.08.006

26. Katzmann JA, Kyle RA, Benson J, et al. Screening panels for detection of monoclonal gammopathies. *Clin Chem*. 2009;55(8):1517-1522. doi:10.1373/clinchem.2009.126664

27. Gavriatopoulou M, Musto P, Caers J, et al. European Myeloma Network recommendations on diagnosis and management of patients with rare plasma cell dyscrasias. *Leukemia*. 2018;32(9):1883-1898. doi:10.1038/s41375-018-0209-7

28. Quarta CC, Gonzalez-Lopez E, Gilbertson JA, et al. Diagnostic sensitivity of abdominal fat aspiration in cardiac amyloidosis. *Eur Heart J*. 2017;38(24):1905-1908. doi:10.1093/eurheartj/ehx047

29. Kimmich C, Schönland S, Kräker S, et al. Amyloid in bone marrow smears in systemic light-chain amyloidosis. *Amyloid*. 2017;24(1):52-59. doi:10.1080/13506129.2017.1314959

30. Mollee P, Renaut P, Gottlieb D, Goodman H. How to diagnose amyloidosis. *Intern Med J*. 2014;44(1):7-17. doi:10.1111/imj.12288

31. Gillmore JD, Maurer MS, Falk RH, et al. Nonbiopsy diagnosis of cardiac transthyretin amyloidosis. *Circulation*. 2016;133(24):2404-2412. doi:10.1161/CIRCULATIONAHA.116.021612

32. Vrana JA, Gamez JD, Madden BJ, Theis JD, Bergen HR III, Dogan A. Classification of amyloidosis by laser microdissection and mass spectrometry-based proteomic analysis in clinical biopsy specimens. *Blood*. 2009;114(24):4957-4959. doi:10.1182/blood-2009-07-230722

33. Gilbertson JA, Theis JD, Vrana JA, et al. A comparison of immunohistochemistry and mass spectrometry for determining the amyloid fibril protein from formalin-fixed biopsy tissue. *J Clin Pathol*. 2015;68(4):314-317. doi:10.1136/jclinpath-2014-202722

34. Kourelis TV, Kyle RA, Dingli D, et al. Presentation and outcomes of localized immunoglobulin light chain amyloidosis: the Mayo Clinic experience. *Mayo Clin Proc*. 2017;92(6):908-917. doi:10.1016/j.mayocp.2017.02.016

35. Geller HI, Singh A, Mirto TM, et al. Prevalence of monoclonal gammopathy in wild-type transthyretin amyloidosis. *Mayo Clin Proc*. 2017;92(12):1800-1805. doi:10.1016/j.mayocp.2017.09.016

36. Dittrich T, Benner A, Kimmich C, et al. Performance analysis of AL amyloidosis cardiac biomarker staging systems with special focus on renal failure and atrial arrhythmia. *Haematologica*. 2019;104(7):1451-1459. doi:10.3324/haematol.2018.205336

37. Dispenzieri A, Gertz MA, Kyle RA, et al. Serum cardiac troponins and N-terminal pro-brain natriuretic peptide: a staging system for primary systemic amyloidosis. *J Clin Oncol*. 2004;22(18):3751-3757. doi:10.1200/JCO.2004.03.029

38. Kumar S, Dispenzieri A, Lacy MQ, et al. Revised prognostic staging system for light chain amyloidosis incorporating cardiac biomarkers and serum free light chain measurements. *J Clin Oncol*. 2012;30(9):989-995. doi:10.1200/JCO.2011.38.5724

39. Palladini G, Sachchithanantham S, Milani P, et al. A European collaborative study of cyclophosphamide, bortezomib, and dexamethasone in upfront treatment of systemic AL amyloidosis. *Blood*. 2015;126(5):612-615. doi:10.1182/blood-2015-01-620302

40. Kyriakou P, Mouselimis D, Tsarouchas A, et al. Diagnosis of cardiac amyloidosis: a systematic review on the role of imaging and biomarkers. *BMC Cardiovasc Disord*. 2018;18(1):221. doi:10.1186/s12872-018-0952-8

41. Grogan M, Scott CG, Kyle RA, et al. Natural history of wild-type transthyretin cardiac amyloidosis and risk stratification using a novel staging system. *J Am Coll Cardiol*. 2016;68(10):1014-1020. doi:10.1016/j.jacc.2016.06.033

42. Gillmore JD, Damy T, Fontana M, et al. A new staging system for cardiac transthyretin amyloidosis. *Eur Heart J*. 2018;39(30):2799-2806. doi:10.1093/eurheartj/ehx589

43. Jaccard A, Moreau P, Leblond V, et al; Myélome Autogreffe (MAG) and Intergroupe Francophone du Myélome (IFM) Intergroup. High-dose melphalan versus melphalan plus dexamethasone for AL amyloidosis. *N Engl J Med*. 2007;357(11):1083-1093. doi:10.1056/NEJMoa070484

44. Sidiqi MH, Aljama MA, Buadi FK, et al. Stem cell transplantation for light chain amyloidosis: decreased early mortality over time. *J Clin Oncol*. 2018;36(13):1323-1329. doi:10.1200/JCO.2017.76.9554

45. Varga C, Comenzo RL. High-dose melphalan and stem cell transplantation in systemic AL amyloidosis in the era of novel anti-plasma cell therapy: a comprehensive review. *Bone Marrow Transplant*. 2019;54(4):508-518. doi:10.1038/s41409-018-0284-4

46. Cibeira MT, Bladé J. Upfront CyBorD in AL amyloidosis. *Blood*. 2015;126(5):564-566. doi:10.1182/blood-2015-06-648113

47. Palladini G, Milani P, Foli A, et al. Oral melphalan and dexamethasone grants extended survival with minimal toxicity in AL amyloidosis: long-term results of a risk-adapted approach. *Haematologica*. 2014;99(4):743-750. doi:10.3324/haematol.2013.095463

48. Kastritis E, Leleu X, Arnulf B, et al. A randomized phase III trial of melphalan and dexamethasone (MDex) versus bortezomib, melphalan and dexamethasone (BMDex) for untreated patients with AL amyloidosis. *Blood*. 2016;128(22):646-646. doi:10.1182/blood.V128.22.646.646

49. Palladini G, Jaccard A, Milani P, et al. Circulating free light chain measurement in the diagnosis, prognostic assessment and evaluation of response of AL amyloidosis: comparison of Freelite and N latex FLC assays. *Clin Chem Lab Med*. 2017;55(11):1734-1743. doi:10.1515/cclm-2016-1024

50. Palladini G, Sachchithanantham S, Milani P, et al. A European collaborative study of cyclophosphamide, bortezomib, and dexamethasone in upfront treatment of systemic AL amyloidosis. *Blood*. 2015;126(5):612-615. doi:10.1182/blood-2015-01-620302

51. Muchtar E, Dispenzieri A, Lacy MQ, et al. Overuse of organ biopsies in immunoglobulin light chain amyloidosis (AL): the consequence of failure of early recognition. *Ann Med*. 2017;49(7):545-551. doi:10.1080/07853890.2017.1304649

52. Dispenzieri A, Kastritis E, Wechalekar AD, et al Primary results from the phase 3 tourmaline-al1 trial of ixazomib-dexamethasone versus physician's choice of therapy in patients (Pts) with relapsed/refractory primary systemic al amyloidosis (RRAL). *Blood*. 2019;134(supplement 1):139-139. doi:10.1182/blood-2019-124409

53. Palladini G, Milani P, Foli A, et al. A phase 2 trial of pomalidomide and dexamethasone rescue treatment in patients with AL amyloidosis. *Blood*. 2017;129(15):2120-2123. doi:10.1182/blood-2016-12-756528

54. Bochtler T, Hegenbart U, Kunz C, et al. Translocation t(11;14) is associated with adverse outcome in patients with newly diagnosed AL amyloidosis when treated with bortezomib-based regimens. *J Clin Oncol*. 2015;33(12):1371-1378. doi:10.1200/JCO.2014.57.4947

55. Bochtler T, Hegenbart U, Kunz C, et al. Prognostic impact of cytogenetic aberrations in AL amyloidosis patients after high-dose melphalan: a long-term follow-up study. *Blood*. 2016;128(4):594-602. doi:10.1182/blood-2015-10-676361

56. Trial of venetoclax (ABT-199) and dexamethasone for relapsed or refractory systemic AL amyloidosis. ClinicalTrials.gov identifier: NCT03000660. Updated May 3, 2019. Accessed June 9, 2020. https://clinicaltrials.gov/ct2/show/NCT03000660

57. Popat R, Dowling E, Achhala S, et al. Real world data of the impact of first cycle daratumumab on multiple myeloma and AL amyloidosis services. *Br J Haematol*. 2018;182(6):936-939. doi:10.1111/bjh.14897

58. Kaufman GP, Schrier SL, Lafayette RA, Arai S, Witteles RM, Liedtke M. Daratumumab yields rapid and deep hematologic responses in patients with heavily pretreated AL amyloidosis. *Blood*. 2017;130(7):900-902. doi:10.1182/blood-2017-01-763599

59. A study to evaluate the efficacy and safety of daratumumab in combination with cyclophosphamide, bortezomib and dexamethasone (CyBorD) compared to cybord alone in newly diagnosed systemic amyloid light-chain (AL) amyloidosis. ClinicalTrials.gov identifier: NCT03201965. Updated May 1, 2020. Accessed June 9, 2020. https://clinicaltrials.gov/ct2/show/NCT03201965

60. Comenzo R, Kastritis E, Maurer MS, et al. Subcutaneous daratumumab+cyclophosphamide, bortezomib and dexamethasone (CYBORD) in patients with newly diagnosed amyloid light chain (AL) amyloidosis. Abstract presented at: European Hematology Association Meeting; June 15, 2019; Amsterdam, the Netherlands.

61. Palladini G, Dispenzieri A, Gertz MA, et al. New criteria for response to treatment in immunoglobulin light chain amyloidosis based on free light chain measurement and cardiac biomarkers: impact on survival outcomes. *J Clin Oncol*. 2012;30(36):4541-4549. doi:10.1200/JCO.2011.37.7614

62. Milani P, Basset M, Russo F, Foli A, Merlini G, Palladini G. Patients with light-chain amyloidosis and low free light-chain burden have distinct clinical features and outcome. *Blood*. 2017;130(5):625-631. doi:10.1182/blood-2017-02-767467

63. Sachchithanantham S, Roussel M, Palladini G, et al. European collaborative study defining clinical profile outcomes and novel prognostic criteria in monoclonal immunoglobulin m-related light chain amyloidosis. *J Clin Oncol*. 2016;34(17):2037-2045. doi:10.1200/JCO.2015.63.3123

64. Muchtar E, Dispenzieri A, Leung N, et al. Depth of organ response in AL amyloidosis is associated with improved survival: grading the organ response criteria. *Leukemia*. 2018;32(10):2240-2249. doi:10.1038/s41375-018-0060-x

65. Dyck PJB, González-Duarte A, Obici L, et al. Development of measures of polyneuropathy impairment in hATTR amyloidosis: from NIS to mNIS + 7. *J Neurol Sci*. 2019;405:116424. doi:10.1016/j.jns.2019.116424

66. Varga C, Lentzsch S, Comenzo RL. Beyond NEOD001 for systemic light-chain amyloidosis. *Blood*. 2018;132(18):1992-1993. doi:10.1182/blood-2018-07-865857

67. Monteiro C, Mesgazardeh JS, Anselmo J, et al. Predictive model of response to tafamidis in hereditary ATTR polyneuropathy. *JCI Insight*. 2019;4(12):126526. doi:10.1172/jci.insight.126526

68. Maurer MS, Schwartz JH, Gundapaneni B, et al; ATTR-ACT Study Investigators. Tafamidis treatment for patients with transthyretin amyloid cardiomyopathy. *N Engl J Med*. 2018;379(11):1007-1016. doi:10.1056/NEJMoa1805689

69. Judge DP, Heitner SB, Falk RH, et al. Transthyretin stabilization by AG10 in symptomatic transthyretin amyloid cardiomyopathy. *J Am Coll Cardiol*. 2019;74(3):285-295. doi:10.1016/j.jacc.2019.03.012

70. Carvalho A, Rocha A, Lobato L. Liver transplantation in transthyretin amyloidosis: issues and challenges. *Liver Transpl*. 2015;21(3):282-292. doi:10.1002/lt.24058

71. Berk JL, Suhr OB, Obici L, et al; Diflunisal Trial Consortium. Repurposing diflunisal for familial amyloid polyneuropathy: a randomized clinical trial. *JAMA*. 2013;310(24):2658-2667. doi:10.1001/jama.2013.283815

72. Benson MD, Waddington-Cruz M, Berk JL, et al. Inotersen treatment for patients with hereditary transthyretin amyloidosis. *N Engl J Med*. 2018;379(1):22-31. doi:10.1056/NEJMoa1716793

73. Adams D, Gonzalez-Duarte A, O'Riordan WD, et al. Patisiran, an RNAi therapeutic, for hereditary transthyretin amyloidosis. *N Engl J Med*. 2018;379(1):11-21. doi:10.1056/NEJMoa1716153

74. Merlini G. AL amyloidosis: from molecular mechanisms to targeted therapies. *Hematology Am Soc Hematol Educ Program*. 2017;2017(1):1-12. doi:10.1182/asheducation-2017.1.1

75. Suzuki T, Kusumoto S, Yamashita T, et al. Labial salivary gland biopsy for diagnosing immunoglobulin light chain amyloidosis: a retrospective analysis. *Ann Hematol*. 2016;95(2):279-285. doi:10.1007/s00277-015-2549-y

76. Moore PT, Burrage MK, Mackenzie E, Law WP, Korczyk D, Mollee P. The utility of ^{99m}Tc-DPD scintigraphy in the diagnosis of cardiac amyloidosis: an Australian experience. *Heart Lung Circ*. 2017;26(11):1183-1190. doi:10.1016/j.hlc.2016.12.017

77. Adams D, Cauquil C, Labeyrie C. Familial amyloid polyneuropathy. *Curr Opin Neurol*. 2017;30(5):481-489. doi:10.1097/WCO.0000000000000476

78. Kristen AV, Dengler TJ, Katus HA. Suspected cardiac amyloidosis: endomyocardial biopsy remains the diagnostic gold-standard. *Am J Hematol*. 2007;82(4):328. doi:10.1002/ajh.20745

79. Obici L, Kuks JB, Buades J, et al; European Network for TTR-FAP (ATTReuNET). Recommendations for presymptomatic genetic testing and management of individuals at risk for hereditary transthyretin amyloidosis. *Curr Opin Neurol*. 2016;29(suppl 1):S27-S35. doi:10.1097/WCO.0000000000000290

80. Wechalekar AD, Gillmore JD, Hawkins PN. Systemic amyloidosis. *Lancet*. 2016;387(10038):2641-2654. doi:10.1016/S0140-6736(15)01274-X

81. Hwa YL, Kumar SK, Gertz MA, et al. Induction therapy pre-autologous stem cell transplantation in immunoglobulin light chain amyloidosis: a retrospective evaluation. *Am J Hematol*. 2016;91(10):984-988. doi:10.1002/ajh.24453

82. Shen KN, Zhang CL, Tian Z, et al. Bortezomib-based chemotherapy reduces early mortality and improves outcomes in patients with ultra-high-risk light-chain amyloidosis: a retrospective case control study. *Amyloid*. 2019;26(2):66-73. doi:10.1080/13506129.2019.1594759